REMARKS

The Invention

The invention features E4orf4-encoding nucleic acids, pharmaceutical compositions and expression vectors containing the same, and methods for their use.

The Office Action

Claims 81-100 are pending. The claims stand rejected for lack of enablement and for being based on an inadequate written description. Claims 88-92 and 95-99 stand rejected for obviousness over Ohgi et al. (J. Biochem. 109:776-785, 1991; hereafter "Ohgi") or Swinkels et al. (Antonie Van Leeuwenhoek 64:187-201, 1993; hereafter "Swinkels") in view of Chroboczek et al. (Virology 186: 280-285, 1992; hereafter "Chroboczek"). Claims 93 and 100 stand rejected for obviousness over Swinkels in view of Miller et al. (FASEB J 9:190-199, 1995; hereafter "Miller") and Chroboczek. The declaration was deemed defective because there was no signature of Josee Lavoie. A new declaration is enclosed herewith.

Rejections Under 35 U.S.C. § 112, first paragraph

Enablement

Claims 81-100 were rejected for lack of enablement. The Examiner acknowledged that "stimulating apoptosis *in vitro* by using a plasmid comprising nucleotide sequence of the disclosed SEQ ID NO: 3 encoding E4orf4" is enabled. According to the Examiner,

however, the specification is not enabling for (i) *in vivo* gene therapy methods; (ii) the use of any expression vector; or (iii) the use of any E4orf4 polypeptide other than that having the sequence of SEQ ID NO.: 4. Applicants respectfully traverse this rejection.

Gene therapy and expression vectors

The Examiner states that the claims were not enabled because "the state of the prior art was not well developed and was highly unpredictable at the time of the invention." Following this line of reasoning, the Examiner then asserts that there were numerous obstacles (e.g., lack of efficient delivery systems, lack of sustained expression) to performing clinical gene therapy on humans and, therefore, the claims lack enablement.

Claims 81-100 are directed to methods and reagents for "increasing apoptosis." The Examiner is reading into the claim term "increasing apoptosis" restrictions which the claim does not contain. Increasing apoptosis is simply the augmentation of the number of cells to undergo apoptosis relative to an untreated control. They are not more narrowly drawn to a method of eliminating or preventing disease.

Thus, in the present case, the proper determination for enablement is whether one skilled in the art could increase cell apoptosis without undue experimentation.

According to In re Wands, 858 F.2d 731, 737, (Fed Cir. 1988):

> Factors to be considered in determining whether a disclosure would require undue experimentation" include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification teaches a method for increasing apoptosis in a cell by introducing into the cell a nucleic acid encoding an adenoviral E4orf4 protein. Specific methods for introducing the E4orf4-encoding nucleic acid are described on page 36, line 22, to page 37, line 15, and on page 49, line 21, to page 52, line 4, of the specification. Moreover, as stated in the specification, the expression vectors described on page 50, line 18, to page 51, line 9 (*e.g.*, retroviral vectors, adenoviral vectors, adeno-associated viral vectors) and methods of their use for expressing foreign genes in cell *in vivo* were generally known at the time of filing. It is axiomatic that the specification need not describe, and preferably omits, that which is well-known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1446 (Fed. Cir. 1986).

One method of expressing an E4orf4 protein in a cell involves the use of adenoviral vectors to express a nucleic acid sequence encoding the E4orf4 protein under the expression of a suitable promoter. Working examples of the use of E4orf4 to increase apoptosis are provided, for example, on page 29, line 26, to page 31, line 4, of the specification, and Applicants proposed that the same mechanism that increased apoptosis *in vitro* would also increase apoptosis *in vivo*.

In support this contention, Applicants submitted, with the previous reply, a declaration from Philip Branton, Ph.D., an inventor on the above-captioned application,

describing experiments in which an adenoviral expression vector containing a nucleic acid encoding E4orf4 was administered to mice having subcutaneous implants of H1299 lung carcinoma cells or C33A cervical carcinoma cells. As is shown in Exhibits A and B and summarized in paragraph 3 of the declaration, adenovirally-mediated expression of E4orf4 resulted in reduced tumor growth relative to control mice. The foregoing findings demonstrate that E4orf4 functions *in vivo* to increase apoptosis of tumor cells. Additionally, paragraph 4 of the Declaration demonstrates that the mouse models used in the foregoing example are well-accepted as indicative of success by those skilled in the art for therapeutic use in other mammals, including humans.

E4orf4 polypeptides

The Examiner asserts that the claims lack enablement because the claims are directed to any E4orf4-encoding nucleic acid having about 50% or greater nucleotide sequence identity with the DNA sequence of SEQ ID NO: 3. Applicants have amended claims 81, 84, 88, 89, 95, and 96, and canceled claims 82, 83, 90, 91, 97, and 98, and this basis for the rejection of the claims for lack of enablement may be withdrawn.

In view of the foregoing remarks, Applicants respectfully request that the rejection of the claims for lack of enablement be withdrawn.

Written Description

Claims 81-100 were also rejected for being based on an inadequate written description. Applicants have met this rejection by amendment of claims 81, 84, 88, 89, 95, and 96 and cancellation of claims 82, 83, 90, 91, 97, and 98. Accordingly, this rejection may also be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 88-92 and 95-99 were rejected for obviousness over Ohgi in view of Chroboczek or for obviousness over Swinkels in view of Chrobozek. Applicants respectfully traverse this rejection.

The M.P.E.P. § 2143 states that to establish a *prima facie* case of obviousness, the prior art references must teach or suggest all of the claim limitations. As is described below, the references cited by the Examiner fail to do so.

Each of the independent claims requires that the polypeptide-encoding nucleic acid be operably linked to a heterologous regulatory sequence for expression of the polypeptide in a mammalian cell (see, e.g., claims 88, 89, 95 and 96). Such a regulatory sequence is neither taught nor suggested by any of the references cited by the Examiner. Ohgi describes the expression of a fungal RNase in a yeast cell using a yeast glyceraldehyde 3-phosphate dehydrogenase promoter. Swinkel describes promoters and expression systems for use in yeast cells. Chroboczek describes the sequencing of genome of Ad5 serotype and its comparison with the genome of Ad2 serotype. Like Ohgi

and Swinkel, Chroboczek fails to teach or suggest a heterologous regulatory sequence for expression of the polypeptide in a mammalian cell.

Additionally, Applicants note that none of the references provides a motivation to even express E4orf4 in a mammalian cell. Until Applicants' discovery that E4orf4 alone was capable of increasing apoptosis, no mammalian cellular function was ascribed to adenoviral E4orf4. Without any appreciation of a function for E4orf4 in mammalian cells, there would have been no motivation to operably link an E4orf4-encoding nucleic acid to heterologous regulatory sequence for expression of the polypeptide in a mammalian cell. For the foregoing reasons, claims 88-93 and 96-99 are nonobvious over any combination of Ohgi, Swinkel, and Chroboczek.

Claims 93 and 100 were rejected for obviousness over Swinkels in view of Miller and Chroboczek.

Like claims 88, 89, 95, and 96, claims 93 and 100 require that an E4orf4-encoding nucleic acid be operably linked to heterologous regulatory sequence for expression of the polypeptide in a mammalian cell. As is discussed above, neither Chroboczek nor Swinkels teaches or suggests the use of a heterologous regulatory sequence for expression of a polypeptide in a mammalian cell. This deficiency is not remedied by Miller. Accordingly, Applicants respectfully request that the rejection of the claims for obviousness be withdrawn.

Conclusion

Applicants submit that the claims are now in condition for allowance, and such action is respectfully requested. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: February 4, 2002

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Enclosures

Marked-up version of claims showing changes made

81. (Amended) A method of inducing apoptosis of a cell, said method comprising expressing in said cell a nucleic acid [having 50% or greater nucleotide sequence identity to the nucleotide sequence of SEQ ID NO.: 3 and] encoding a polypeptide comprising the sequence of SEQ ID NO.: 4 and capable of inducing apoptosis, said nucleic acid operably linked to a heterologous regulatory sequence for expression of said polypeptide, wherein expressing said nucleic acid in said cell induces apoptosis of said cell.

84. (Amended) A method of inducing apoptosis of a cell, said method comprising expressing in said cell a nucleic acid [capable of hybridizing at high stringency to the complement of the nucleic acid of SEQ ID NO.: 3 and] encoding a polypeptide having the sequence of SEQ ID NO.: 4 and capable of inducing apoptosis, said nucleic acid operably linked to a heterologous regulatory sequence for expression of said polypeptide, wherein expressing said nucleic acid in said cell induces apoptosis of said cell.

88. (Amended) A pharmaceutical composition comprising (i) an expression vector comprising a [substantially purified] nucleic acid [capable of hybridizing at high stringency to the complement of the nucleic acid of SEQ ID NO.: 3 and] encoding a polypeptide comprising the sequence of SEQ ID NO.: 4 and capable of inducing apoptosis, and (ii) a pharmaceutically acceptable carrier, wherein said nucleic acid is operably linked to a heterologous regulatory sequence for expression of said polypeptide in a mammalian cell.

89. (Amended) A pharmaceutical composition comprising (i) an expression vector comprising a nucleic acid [having 50% or greater nucleotide sequence identity to the nucleotide sequence of SEQ ID NO.: 3 and] encoding a polypeptide having the sequence of SEQ ID NO.: 4 and capable of inducing apoptosis, and (ii) a pharmaceutically acceptable carrier, wherein said nucleic acid is operably linked to a heterologous regulatory sequence for expression of said polypeptide in a mammalian cell.

95. (Amended) An expression vector comprising a nucleic acid [capable of hybridizing at high stringency to the complement of the nucleic acid of SEQ ID NO.: 3 and] encoding a polypeptide comprising the sequence of SEQ ID NO.: 4 and capable of inducing apoptosis, wherein said nucleic acid is operably linked to a heterologous regulatory sequence for expression of said polypeptide in a mammalian cell.

96. (Amended) An expression vector comprising a nucleic acid [having 50% or greater nucleotide sequence identity to the nucleotide sequence of SEQ ID NO.: 3 and]

encoding a polypeptide having the sequence of SEQ ID NO.: 4 and capable of inducing apoptosis, wherein said nucleic acid is operably linked to a heterologous regulatory sequence for expression of said polypeptide in a mammalian cell.